REMARKS

1.Introduction

Claims 1-84 are currently pending in this application. Following entry of these amendments, claims 1-6, 22-29, 32-33, 35, 37-42, 52-59, 62, and 85-104 will be pending.

2. Basis for New Claims

No new matter is introduced into the specification by way of these amendments. New claims 85-104 find support throughout the specification as originally filed.

New claims 85-87 find support in the specification as originally filed, for example, on page 4, lines 19-20.

New claim 88 finds support in the specification as originally filed, for example, on page 41, Example 1, lines 14-15, page 7, lines 13-14 and Figure 1.

New claims 89-90 finds support in the specification as originally filed, for example, on page on page 17, lines 10-21.

New claim 91 finds support in the specification as originally filed, for example, on page 9, lines 24-26.

New claim 92 find support in the specification as originally filed, for example, on page 9, lines 4-7.

New claim 93 finds support in the specification as originally filed, for example, on page 28, lines 23-29 and claim 6.

New claims 94-97 find support in the specification as originally filed, for example, on page 4, lines 19-20.

New claim 98 finds support in the specification as originally filed, for example, on page 41, Example 1, lines 14-15, page 7, lines 13-14 and Figure 1.

New claims 99-100 find support in the specification as originally filed, for example, on page 17, lines 10-21.

New claim 101 finds support in the specification as originally filed, for example, on page 9, lines 24-26.

New claim 102 find support in the specification as originally filed, for example, on page 9, lines 4-7.

New claim 103 finds support in the specification as originally filed, for example, on page 37, lines 19-27 and claim 33.

New claim 104 finds support in the specification as originally filed, for example, on page 31, lines 16-20.

3. Description Issues

3.1. The Examiner rejected claims 1-62 under 35 U.S.C. § 112 first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time of filing, had possession of the claimed invention. More specifically, the Examiner has stated that only Apo A-I, Apo-A-II Apo-A-IV or Apo-E

meets the written description requirements of 35 U.S.C. § 112 first paragraph.

Applicants have amended rejected claims 1-62 by deleting the wording "*a functional analogue or variant thereof*", thereby limiting the claims to apolipoprotein A-I, A-II and A-IV, and accordingly have mooted this rejection.

3.2. The Examiner also rejected claims 27-29, 35-36, 57-59 and 62 under 35 U.S.C. § 112, first paragraph for lack of description. More specifically, the Examiner asserts that there is no description of the relationship between the percent similarity (e.g. 68% or 70%) the specific biological function. The Examiner suggest amending the claim to delete the 68% or 70% identity language and indicate a specific, measurable function.

Applicants have amended rejected claims 27-29, by inserting the wording: "*and is capable of forming a stable trimeric complex with other tetranectin trimerising modules*" in claims 27 and 29. Similarly, rejected claims 57-59 have been amended by the insertion of the wording "*and is capable of forming a stable trimeric complex with other tetranectin trimerising modules*" in claims 57 and 59. Thereby, the claims have been further limited to tetranectin trimerising modules with a specific measurable property (or activity), namely tetranectin trimerising modules which are capable of forming a stable trimeric complex with other tetranectin trimerising modules. It can be determined by standard methods such as cross-linking followed by SDS-PAGE or analytical gelfiltration if a given

tetranectin trimerising module "*is capable of forming a stable trimeric complex with other tetranectin trimerising modules*", e.g. by performing the analytical steps described in details in the specification on pages 43-44 (Example 5: Multimerisation assay).

Applicants have amended rejected claim 35 (claim 36 has been deleted), by changing the claim dependency from claim 1 to claim 33 and by inserting the wording "*wherein the trimeric complex comprises*". Similarly, Applicants have amended rejected claim 62, by changing the claim dependency from claim 38 to new claim 103. Thereby, the subject matter of these claim has been limited to a specific measurable biological activity, namely the capability of the trimeric complex of binding to a receptor or protein selected from cubilin, megalin, Scavenger receptor class B, type 1 (SR-B1), ATP-binding cassette 1 (ABC1), Lecithin:cholesterol acyltransferase (LCAT), Cholesteryl-ester transfer protein (CETP), and Phospolipid transfer protein (PLTP). Such a test may be carried out as described in more details in the specification, e.g. on page 37, lines 19-27 and in Example 7, page 45, lines 5-16.

It is unclear from the wording of the rejection whether the Examiner would accept percentage identity language if coupled with a biological function constraint. OA page 5, lines 3-6 suggest that he would, but lines 7-8 suggest otherwise.

At the outset, we must point out that the Examiner uses the terms "percentage similarity" and "percentage identity"

interchangeably, contrary to the usage in the art. When the art refers to percentage identity, the only amino acid which counts as a match for Leu is Leu itself, any other aligned AA is a mismatch. When the art refers to percentage similarity, any similar AA is a match, e.g., Ile could be a match for Leu. A program which calculates percentage similarity will have an internal table which identifies the groups of similar AAs.

Claims 27, 29, 35, 57, 59 and 62 all recite percentage identity, the more stringent concept.

The Examiner does not and cannot dispute that the percentage identities recited in these claims are part of the original disclosure.

All of the claims at issue relate to the choice of the tetranectin trimerizing module. Figure 4 shows the natural variation of this module among four tetranectins (human, murine, bovine, shark), as discussed at P9, L11-22, and P30, L12-33.

In Fig. 4, in the subsequence surmounted by "defg...efga", there are only 15 absolutely conserved residues out of a total of 26 AAs. 15/26 corresponds to about 58% identity. If the 8 N-terminal residues and one C-terminal residue outside this marked subsequence are considered, we have 15 identities out of 35 aligned positions, for a percentage identity of about 43%.

Given this precedent, we think that it is reasonably to

expect that sequences at least 68% identical to SEQ ID NO:12 (claim 27) or SEQ ID NO:13 (claim 28) will be functional. To the extent that a pure % identity would capture some inoperative embodiments, this is avoided by coupling the % identity limitation with an activity limitation.

In Ex. 14 of the Written Description Training Materials, the PTO indicates that a claim to a protein at least 95% identical to a reference sequence, which possesses a recited enzymatic activity is adequately "described": "The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity".

Nowhere does the WDTM indicate that it cannot accept a % identity limitation less stringent than 95%. Given the evidence that the tetranectins retains trimerizing activity despite % identities less than 68%, the use of % identity of 68% identity in connection with a known trimerizing element is acceptable under 112/1's description requirement.

Accordingly, applicants respectfully request reconsideration and withdrawal of the rejections of claims 27-29, 35-36, 57-59 and 62 for lack of written description.

4. Definiteness Issues

The Examiner rejected claims 1, 15-30, 38 and 58 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. More specifically, the Examiners asserts that: (i) the term "*construct*" in claims 1 and 38 is indefinite, (ii) the term "*substantially*" in claim 4 renders the claim indefinite, (iii) there is insufficient antecedent basis for the limitation "*the oligomerising module*" in claims 15-30, and (iv) claims 28 and 58 are indefinite because they contain a multiplicity of periods.

Applicants have amended rejected claims 1 and 38, by inserting the term "*protein*".

Applicants have amended rejected claim 4, by deleting the wording "*or substantially linear*".

Applicants have deleted rejected claims 15-21.

Applicants have amended rejected claims 22-30, by i.a. changing the claim dependency from claim 21 to claim 1.

Applicants have amended rejected claims 28 and 58 by deleting the term "*no.*".

Accordingly, applicants believe they have fully addressed the Examiners concerns, and therefore respectfully request reconsideration and withdrawal of the rejections of claims 1, 15-30, 38 and 58 under 35 U.S.C. § 112, second paragraph

as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

5. Prior Art Issues

5.1. The Examiner rejected claims 1-4, 7, 8, 11-14, 32, 33, 35-41, 43-49 and 62 under 35 U.S.C. § 102(b), as allegedly being anticipated by Smith *et al.* (US 5,408,038). More specifically, the Examiner asserts that: (i) Smith *et al.* teach a fusion protein comprising human Apo-B and human Apo AI, (ii) the Apo-B taught by Smith *et al.* is an oligomerizing protein that would be terminally linked to ApoA, (iii) the vector construct taught by Smith *et al.* contains a linker sequence that would translate into two or more amino acids, (iv) ApoB would read upon the limitation of a variant eliciting substantially the same physiological response to Apo AI, (v) the binding of proteins such as CETP is an inherent property of Apo-A, (vi) the composition of Smith *et al.* is taught as a composition that is pharmaceutically acceptable, (vii) the ability of apolipoproteins to oligomerise is an inherent property of the molecules, and (viii) human Apo-B and human Apo AI each have greater than 70% identity with SEQ ID NOs:2, 3, 11 and 14 (per claims 35, 36, 62).

In light of the amendments to claims 1 and 38, Applicants respectfully disagree and traverse this rejection. In order for a reference to anticipate under 35 U.S.C. § 102(b), the reference must disclose all limitations of the claimed invention. Smith *et al.* fails this test.

As amended herein, pending claim 1 recites:

> 1. A pharmaceutical composition comprising an apolipoprotein protein construct having the general formula apo-A-X, where apo-A is an apolipoprotein component selected from the group consisting of apolipoprotein A-I, apolipoprotein A-II, and apolipoprotein A-IV, and X is a tetranectin trimerising module.

Smith *et al.* i.a. disclose a fusion protein consisting of human Apo-B and human Apo AI. However, nowhere in Smith *et al.* has there been disclosed a pharmaceutical composition comprising an apolipoprotein protein construct having the general formula apo-A-X, where apo-A is an apolipoprotein component selected from the group consisting of apolipoprotein A-I, apolipoprotein A-II, and apolipoprotein A-IV, and X is a tetranectin trimerising module.

As a result, Smith *et al.* is not available as proper § 102(b) prior art, as this reference does not meet all the limitations of claim 1. Claims 3-4, 7, 8, 11-14, 32, 33 and 35-37 ultimately incorporate all of the limitations of claim 1 through dependency. Therefore, Smith *et al.* is equally inapplicable as proper § 102(b) prior art against claims 3-4, 7, 8, 11-14, 32, 33 and 35-37.

Similarly, pending claim 38 as amended herein recites:

> 38. An apolipoprotein protein construct having the general formula apo-A-X, where apo-A is an apolipoprotein component selected from the group consisting of apolipoprotein A-I, apolipoprotein A-II,

and apolipoprotein A-IV, and X is a tetranectin trimerising module.

It is respectfully submitted that nowhere in Smith *et al.* has such an apolipoprotein protein construct been disclosed or even suggested. As a result, Smith *et al.* is inapplicable as proper § 102(b) prior art against claim 38. Smith *et al.* is equally inapplicable as proper § 102(b) prior art against claim 39-41, 43-49 and 62, which depend from claim 38.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1-4, 7, 8, 11-14, 32, 33, 35-41, 43-49 and 62 under 35 U.S.C. § 102(b), as allegedly being anticipated by Smith *et al.*

5.2. The Examiner rejected claims 1-4, 6-8, 10-14, 15, 18, 32, 33 and 35-37 under 35 U.S.C. § 102(b), as allegedly being anticipated by Sirtori *et al.* (US 5,876,968). More specifically, the Examiner asserts that (i) Sirtori *et al.* teach apolipoprotein AI-M fused to a modified IgG, (ii) Apo AI-M share greater than 70% identity with SEQ ID NOS 2, 3, 11 and 14, (iii) a major structural element of Apo AI is presumed to exist in a amphipatic helical conformation, (iii) Apo AI-M has the capacity to form dimers with itself and (iv) the protein contains a substantially linear spacer sequence that is cleavable with formic acid.

In light of the above amendments to claim 1, Applicants respectfully disagree and traverse this rejection.

As stated by the Examiner, Sirtori *et al.* i.a. disclose apolipoprotein AI-M fused to a modified IgG. However, it is respectfully submitted that nowhere in Sirtori *et al.* has there been disclosed or suggested a pharmaceutical composition comprising an apolipoprotein protein construct having the general formula apo-A-X, where apo-A is an apolipoprotein component selected from the group consisting of apolipoprotein A-I, apolipoprotein A-II, and apolipoprotein A-IV, and X is a tetranectin trimerising module.

As a result, Sirtori *et al.* is not available as proper § 102(b) prior art against claim 1, as this reference does not meet all the limitations of claim 1. Claims 2-4, 6-8, 10-14, 15, 18, 32, 33 and 35-37 incorporate all of the limitations of claim 1 through dependency. Therefore, Sirtori *et al.* is equally inapplicable as proper § 102(b) prior art against claims 2-4, 6-8, 10-14, 15,18, 32, 33 and 35-37.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1-4, 6-8, 10-14, 15, 18, 32, 33 and 35-37 under 35 U.S.C. § 102(b), as allegedly being anticipated by Sirtori *et al.*

Conclusion

Applicants believe that incorporation of the amendments and consideration of the above remarks have placed this

application in a condition for allowance. Early notification of a favourable consideration is respectfully requested.

Respectfully submitted,

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